PROCESS FOR PREPARATION OF ISOSULFAN BLUE

CROSS-REFERENCE TO RELATED APPLICATIONS

This is a continuation application, and claims the benefit, of U.S. patent application Ser. No. 12/643,056, filed Dec. 21, 2009, which is a continuation of U.S. Ser. No. 12/180,057 filed Jul. 25, 2008, now U.S. Pat. No. 7,662,992, which is a continuation of U.S. Ser. No. 11/747,291 filed May 11, 2007, now abandoned, the entireties of which are incorporated herein by reference.

FIELD OF THE INVENTION

The present invention relates to a process for the production of isosulfan blue, and in particular, to a process for the production of isosulfan blue in a substantially pure form.

BACKGROUND OF THE INVENTION

Isosulfan blue, having a chemical name, N-[4-[[4-(diethyl amino)phenyl](2,5-disulfophenyl)methylene]-2,5-cyclohexadien-1-ylidene]-N-ethylethanaminium, sodium salt and the formula

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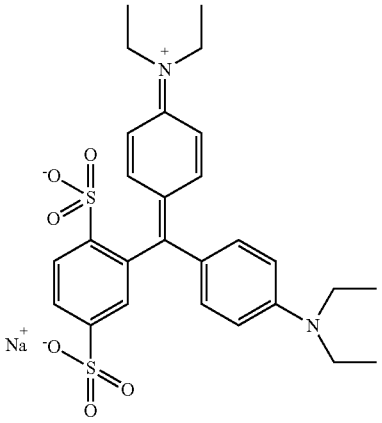

is a triarylmethane dye used as a contrast agent for the delineation of lymphatic vessels and is particularly useful as a cancer diagnostic agent. Also known chemically as sulfan blue or patent blue, isosulfan blue is an active pharmaceutical ingredient used in the Lymphazurin™ blue dye pharmaceutical dosage form, available as 1% (10 mg/ml) 5 ml solution in phosphate buffer for injection. It is commonly used in a procedure called "mapping of the sentinel lymph nodes". It is an adjunct to lymphography for visualization of the lymphatic system draining the region of injection. It has been used with increasing frequency in localizing sentinel lymph nodes in breast cancer patients. Isosulfan blue-guided surgical removal of cancerous tissue has been on the rise as it is cost effective and safer to use than technetium 99M radioisotope-labeled sulfur colloid. Isosulfan blue is a structural isomer of sulphan blue; both belong to the family of triarylmethane dyestuffs. Generally, preparation of triarylmethane dyes involves condensation of suitably substituted aryl aldehydes with 2 equivalents of alkyl-aryl amines giving rise to leuco-bases or leuco-acids followed by oxidation. Although the literature is replete with methods of preparing triarylmethane dyes, most of the methods involve strong acids for condensation resulting in leuco-bases or leuco-acids, hazardous oxidizing agents (lead oxide, chloranil, iron phthalocyanine/oxone) for converting to triarylmethane dyes, and crude methods (precipitation with sodium sulfate) of purification. See for example U.S. Pat. Nos. 4,330,476, 4,710,322, 1,531,507, 5,659,053, 1,805,925, 2,422,445, 1,878,530 and 2,726,252. Prior art methods of isolation of the crude leuco-acids or leuco-bases involve tedious neutralization/basification with strong bases and typically using the reaction mixtures in the oxidation step, giving rise to crude triarylmethane dyes. The triarylmethane dyestuffs thus prepared are used mainly for dyeing fabric, coloring paper, and printing inks. The literature cites utilization of the same aforementioned synthetic and isolation methods for the preparation of diagnostically important dyes, such as isosulfan blue, sulphan blue and patent blue V. See, Rodd's Chemistry of Carbon Compounds by S. Coffey, 1974 2nd Edition, Volume III Part F, 110-133.

Therefore there is a need in the art for an improved method in the process chemistry of isosulfan blue to be prepared in the purest form which is suitable for large scale cGMP production for its pharmaceutical formulation manufacturing.

SUMMARY OF THE INVENTION

It is therefore an object of the present invention is to provide a simple, safe, cost-effective, time saving and reliable process for the preparation of isosulfan blue in bulk scale and in substantially pure form. "Substantially pure" is defined herein as 99.0% or greater.

Another object of the invention is to provide a simple, cost-effective and reliable process for preparation of the intermediate, 2-chlorobenzaldehyde-5-sulfonic acid, sodium salt of formula (2), required in the preparation of isosulfan blue. This embodiment provides a process step that does not require tedious neutralization with very large quantities of sodium carbonate and effervescence, as is the case in prior art processes.

Another object of the invention is to provide a simplified procedure for the isolation of benzaldehyde-2,5-disulfonic acid, di-sodium salt of the formula (3) that does not include acidifying the reaction mixture with concentrated sulfuric acid and boiling until excess sulfurous acid is expelled, as is taught in the prior art.

Yet another object of the invention is to provide a procedure for obtaining the benzaldehyde-2,5-disulfonic acid, sodium salt of formula (3) free of inorganic salts, which essentially simplifies the isolation procedures to be implemented during isolation of isoleuco acid.

Yet another, object of the invention is to provide a process for the preparation of an isoleuco acid of formula (4), through the urea derivative as an in-situ intermediate. The isoleuco acid of formula (4) on further oxidation gives rise to the target compound, isosulfan blue (5). Still another object of the invention is to use very mild oxidation agent to avoid any over oxidized products and also to improve the stability of the isosulfan blue under reaction conditions.

According to this invention, there is provided a simple procedure for the isolation of benzaldehyde-2,5-disulfonic acid, isoleuco acid and isosulfan blue at acid stage and also at sodium salt formation stage by incorporating crystallization techniques, thereby avoiding distillation and other techniques using high temperatures which jeopardize the compound stability during the manufacturing process.